NOT YET SCHEDULED FOR ORAL ARGUMENT

No. 12-5349

In the United States Court of Appeals for the District of Columbia Circuit

KV PHARMACEUTICAL COMPANY;
THER-RX CORPORATION,
APPELLANTS

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION;
UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES;
MARGARET HAMBURG, M.D., COMMISSIONER OF FOOD AND DRUGS;
KATHLEEN SEBELIUS, SECRETARY OF HEALTH & HUMAN SERVICES,
APPELLEES

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DISTRICT OF COLUMBIA (CIV. NO. 12-1105) (THE HONORABLE AMY BERMAN JACKSON, J.)

CORRECTED REPLY BRIEF OF APPELLANTS KV PHARMACEUTICAL COMPANY AND THER-RX CORPORATION

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SUMMARY OF ARGUMENT

The Brief for Appellees ("FDA Brief") does not deny that the Food and Drug Administration ("FDA") issued its March 30, 2011 statement (the "Statement") in response to political pressure from Senator Sherrod Brown and others that FDA do "something" to lower the price of hydroxyprogesterone caproate ("HPC" or "17P"[1]), *see* Brief of Appellants K-V Pharmaceutical Company and Ther-Rx Corporation ("KV Brief") 16-17. Thus, it does not deny that the Statement was issued to affect drug pricing – an impermissible purpose, *see id.* at 9 & n.18.

The Statement's issuance under political pressure to bring about a lower price makes clear that it is an active solicitation of unlawful distribution of uncustomized 17P.[2] Its self-evident strategy "to support access," Appendix ("JA") 233, is to drive down the price of HPC, and thereby relieve the political pressure, by inducing "compounders" (really, unapproved manufacturers) to manufacture and distribute on a commercial scale versions of 17P that have a lower price than Makena® because the "compounders" do not comply with the requirements of the Federal Food, Drug, and Cosmetic Act ("FDCA"), *e.g.*, the approval requirements,

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[1] Here, "17P" means HPC purporting to be compounded.

[2] "Uncustomized" means not customized to meet a "patient-specific medical need," *see infra* note 9.

21 U.S.C. § 355, and requirements concerning manufacturing practices, 21 U.S.C. § 351(a)(2)(B); 21 C.F.R. pts. 210, 211 (2012), and adverse-event reporting, 21 C.F.R. § 314.80 (2012); *see also* 21 U.S.C. § 355b. Appellees offer no alternative explanation of the Statement.

Appellees contend, without supporting analysis, that KV has "no basis to assert that compounding of 17P after March 2011 'would not have occurred if FDA had done nothing.' Pl. Br. 25 (underlining omitted)." FDA Brief 32. Appellees fail to address the evidence presented at KV Brief 6 that uncustomized "compounding" of 17P would not have occurred had FDA done nothing. Traditional customized compounding would have occurred without FDA action, and without objection by KV.

ARGUMENT

I. FDA'S STATEMENT AND POLICY ARE REVIEWABLE.

A. This Case Is Outside the Framework of *Heckler v. Chaney*.[3]

1. FDA's Statement Involves Active Solicitation of Unlawful Conduct, Not Merely Non-Enforcement.

Chaney distinguished "an affirmative act of approval" from non-enforcement. 470 U.S. at 831. *See also Transp. Intelligence, Inc. v. FCC*, 336 F.3d 1058, 1063 (D.C. Cir. 2003) (same).

[3] 470 U.S. 821 (1985).

Contrary to FDA Brief 26, FDA's Statement does not announce a decision not to take enforcement action against exogenous past conduct, but, rather, functions as an approval of multiple versions of uncustomized 17P and their future distribution in interstate commerce. The Statement is "an affirmative act" because it is a press release plainly intended to change the *status quo* by eliciting future conduct. Although the Statement does not make uncustomized 17P lawful, it makes unlawfulness irrelevant. It authorizes "compounders" to manufacture and distribute on a commercial scale uncustomized versions of 17P. In express reliance on that authorization, the Centers for Medicare & Medicaid Services ("CMS") advises how Medicaid agencies can pay for those drugs, JA235.

Under 21 U.S.C. § 355(a), what an approval authorizes is interstate distribution. Thus, although the Statement notes that an approved product has a "greater assurance of safety," JA233, the essence of an approval is the authorization of distribution, not the "greater assurance of safety." Even without that assurance, FDA's Statement supports reimbursement, JA235, and, together with CMS's bulletin, has elicited so much substitution of 17P for Makena that KV is in bankruptcy. *See* KV Brief 21. Title 21 U.S.C. § 360cc(a) is intended to provide patent-like protection for approved orphan drugs against competition during their respective exclusivity periods. FDA's functional approval of unlawful distribution destroys that protection.

Appellees assert that the "Statement does not differ in any relevant way from the FDA statement regarding its enforcement against lethal injection drugs in *Chaney,* and it does not represent a disavowal of 'an intention to proceed against compounding pharmacies as a general matter.' JA83." FDA Brief 30. Not so.

Contrary to FDA Brief 31-32, the contexts differ materially. In *Chaney*, FDA issued a decision letter in response to a citizen petition.[4] FDA did not publicize its position or solicit future conduct. Here, to relieve political pressure, FDA issued a press release to maximize dissemination of the Statement "to support access" by soliciting unlawful future distribution of uncustomized 17P.[5] FDA's Statement and CMS's bulletin jointly invite a flooding of the market with such versions of 17P, and communicate that Medicaid can pay for them (partly with federal funds[6]). *See* KV Brief 23-28. There was nothing analogous in *Chaney*.

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[4] *See Chaney v. Heckler*, 718 F.2d 1174, 1177-78 (D.C. Cir. 1983), *rev'd on other grounds,* 470 U.S. 821 (1985).

[5] In *Chaney*, the use of approved drugs off-label was lawful. *See* Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,733 (June 9, 1983). Indeed, without the "greater assurance of safety" FDA provides for approved uses of a drug, "off-label" prescribing "occurs frequently." GAO, Prescription Drugs[:] FDA's Oversight of the Promotion of Drugs for Off-Label Uses 2 (July 2008), *available at* http://www.gao.gov/assets/280/278832.pdf. The key is that the drugs are distributed, and therefore available.

[6] *See generally* 42 U.S.C. § 1396b; CMS, Financing & Reimbursement, *available at* http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Financing-and-Reimbursement/Financing-and-Reimbursement.html (last visited June 4, 2013).

FDA's Statement is, indeed, a disavowal of an intention to proceed against "compounders" of uncustomized 17P as a general matter. It is so understood by Wedgewood Village Pharmacy ("Wedgewood"), "one of the largest compounding pharmacies in the United States," serving "more than 25,000 prescribers": "With FDA green light, Wedgewood Pharmacy continues to compound 17P." JA239. FDA has taken no enforcement action to counter that understanding.

Appellees assert, without supporting analysis:

> plaintiffs have no basis to assert that compounding of 17P after March 2011 "would not have occurred if FDA had done nothing." Pl. Br. 25 (underlining omitted). In no sense was "FDA's issuance of a press release . . . the equivalent of an order or license." Pl. Br. 27 (underlining omitted). FDA's since-superseded March statement did not authorize, solicit, or call forth unlawful compounding.

FDA Brief 32. Appellees fail to confront (i) the fact that FDA issued its Statement as a press release, JA233; (ii) the Statement's political context, KV Brief 14-17; and (iii) "compounder" reaction to it, KV Brief 6 & nn.11, 12. Eliciting additional distribution of uncustomized 17P was a means for Appellees to drive down the price of HPC to relieve the political pressure on them. Thus, the only plausible interpretation of the Statement is that Appellees intended it to call forth, and that it does call forth, and thereby authorizes and invites, future distribution of uncustomized 17P. Appellees solved their political problem at KV's expense and at increased risk to the pregnant women for whom Makena is indicated (and their

fetuses). The Statement has not been superseded and remains operative. *See infra* pp. 10-21.

The Statement refers to letters KV had sent, JA215-19. The letters reflected the same understanding of how FDA's enforcement policies apply to 17P that Wedgewood articulated, *see* JA239; KV Brief 6 & n.11, and that FDA's warning letters to "compounders" articulate, *see infra* pp. 12-13. The letters contained no error. Appellees cite no precedent for the Statement's departure from FDA's long-established compliance policies concerning the distribution of unapproved new drugs and compounded drugs, *see* KV Brief 13, 25 n.43. When FDA decided to depart from those policies, it could have asked KV to send follow-up letters to the recipients of its original letters. Plainly, however, FDA wanted to reach the largest possible audience – all "compounders" – to elicit large amounts of 17P. So, it issued a press release.

Appellees' reliance on *Teva Pharmaceutical Industries Ltd. v. Crawford*, 410 F.3d 51 (D.C. Cir. 2005), FDA Brief 26-27, is unavailing. *Teva* did not reject functional interpretations in principle, but merely Teva's particular interpretation. An interpretation that would preclude FDA from authorizing distribution of uncustomized "compounded" drugs to destroy orphan-drug exclusivity is distinguishable from Teva's proposed prohibition of authorized generic drugs.

First, an authorized generic drug is an already approved drug – identical to the approved brand-name drug, except in external packaging, labeling, and/or price.[7] Therefore, FDA has already authorized its distribution; no further FDA action is needed. Teva sought to bar the distribution of an approved drug. Here, the uncustomized "compounded" drugs were unapproved before the Statement. Further FDA action – the Statement – was needed to authorize their distribution.

Second, there was no prohibition of authorized generic drugs when the Hatch-Waxman Amendments, Pub. L. No. 98-417, 98 Stat. 1585 (1984), were enacted. 410 F.3d at 54. Here, before enactment of the Orphan Drug Act ("ODA"), Pub. L. No. 97-414, 96 Stat. 2049 (1983), caselaw, cited at JA100, established that the FDCA prohibits the distribution of uncustomized "compounded" drugs.

Third, unlike generic-drug exclusivity in *Teva*, which did not protect against competition from the previously approved brand-name drug, orphan-drug exclusivity protects against all versions (brand-name and generic) labeled for the same indication. Pre-ODA caselaw made it unnecessary for Congress to legislate against uncustomized "compounded" drugs competing with an approved orphan drug during its exclusivity period. KV Brief 45-46.

[7] *See* 21 C.F.R. § 314.3(b) (2012) (defining "[a]uthorized generic drug").

2. FDA's Statement Announces a Policy, Not a Single-Shot Decision.

For almost two decades, it has been established in this Circuit that *Chaney* is limited to single-shot enforcement decisions, and is inapplicable to general enforcement policies. *See* KV Brief 21-34.

Appellees err in denying that *Crowley Caribbean Transport, Inc. v. Peña*, 37 F.3d 671 (D.C. Cir. 1994), holds that "statements of general enforcement policy, as distinct from case-specific enforcement decisions, are subject to judicial review notwithstanding *Chaney*," FDA Brief 28. "[A]n agency's adoption of a general enforcement policy is subject to review. Indeed, in *Crowley Caribbean Transport*, this court distinguished between 'an agency's statement of a *general enforcement policy*' and a '*single-shot* nonenforcement decision,' the former being reviewable even though the latter may not be." *OSG Bulk Ships, Inc. v. United States*, 132 F.3d 808, 812 (D.C. Cir. 1998).

Appellees argue that, under *Crowley* and *OSG*, "the relief a court can grant is clear: the court may correct legal error, and an agency may then exercise any relevant enforcement discretion without the impediment of a misconception of the agency's legal authority to act." FDA Brief 29. That argument fails to help Appellees.

The reviewability of general statements of enforcement policy is not limited to statements based on statutory interpretations. *See* KV Brief 35-36. Moreover,

contrary to FDA Brief 30, here, FDA's Statement raises at least two issues of statutory interpretation: (i) whether Section 360cc(a) permits FDA to authorize distribution of uncustomized "compounded" drugs to defeat the grant of exclusivity to the sponsor and drive down the price, and (ii) whether 21 U.S.C. § 381(a) permits FDA to allow imports of an unapproved active pharmaceutical ingredient ("API") to support such "compounding." If KV obtains the relief requested, FDA may exercise enforcement discretion concerning individual "compounders" without the impediment of a misconception of its authority to elicit unlawful "compounding" to drive down the price of an orphan drug with statutory exclusivity; and FDA will be barred from allowing, in aid thereof, imports that appear to be unlawful. Moreover, Section 360cc(a)'s incentive for orphan drug development will be restored by protection of the statutorily mandated grant of exclusivity.

Contrary to FDA Brief 22-23, *Jerome Stevens Pharmaceuticals, Inc. v. FDA,* 402 F.3d 1249 (D.C. Cir. 2005), and *Schering Corp. v. Heckler*, 779 F.2d 683 (D.C. Cir. 1985), are distinguishable. *See* KV Brief 39 n.55. Each involved a deferral of enforcement limited as to time and parties. Those are critical distinctions because the timing and scope of particular enforcement actions are within an agency's discretion, if the agency is neither applying an unlawful policy nor abdicating its enforcement responsibility. Here, FDA's announced non-

enforcement policy is unlawful and an abdication. It is unlimited as to time and parties: it applies indefinitely to the thousand-plus current "compounders," *see* KV Brief 18 & n.37, and to any and all new start-up "compounders."

Moreover, *Schering* addressed a challenge to a settlement between FDA and one company in one case involving one product. The instant case involves multiple "compounders" and expanded and new distribution of multiple products (each version of 17P is a separate product).

3. FDA Is Not Applying Its Established Enforcement Policies to Uncustomized 17P, But Continues To Apply the Non-Enforcement Policy Announced in Its March 30, 2011 Statement.

Appellees assert that FDA's "June 2012 Statement further affirms that FDA 'is applying its normal enforcement policies for compounded drugs to compounded [17P].' JA274." FDA Brief 23-24 (brackets in original); *see also id.* at 26 (same). FDA is not doing so.

Two FDA enforcement policies should apply here: FDA, Guidance for FDA Staff and Industry[:] Marketed Unapproved Drugs – Compliance Policy Guide § 440.100[:] Marketed Drugs Without Approved NDAs or ANDAs (June 2006) ("CPG 440.100"), JA243-50,[8] and FDA, Compliance Policy Guidance for FDA

[8] An "NDA" is a new drug application; an "ANDA" is an abbreviated NDA (for a generic drug).

Staff and Industry[:] Pharmacy Compounding § 460.200 (May 2002) ("CPG 460.200"), JA161-67. FDA is applying neither one to uncustomized 17P.

CPG 440.100 states FDA's enforcement policy concerning marketed unapproved drugs:

> Sometimes, a company may obtain approval of an NDA for a product that other companies are marketing without approval.[10] We want to encourage this type of voluntary compliance with the new drug requirements because it benefits the public health by increasing the assurance that marketed drug products are safe and effective — it also reduces the resources that FDA must expend on enforcement. Thus, because they present a direct challenge to the drug approval system, FDA is more likely to take enforcement action against remaining unapproved drugs in this kind of situation. However, we intend to take into account the circumstances once the product is approved in determining how to exercise our enforcement discretion with regard to the unapproved products. In exercising enforcement discretion, we intend to balance the need to provide incentives for voluntary compliance against the implications of enforcement actions on the marketplace and on consumers who are accustomed to using the marketed products.
>
> When a company obtains approval to market a product that other companies are marketing without approval, FDA normally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type. However, the grace period provided is expected to vary from this baseline based upon the following factors . . . .

[10] These may be products that are the same as the approved product or somewhat different, such as products of different strength.

JA245-46 (footnote omitted). This policy gives major weight to protecting the incentive for drug manufacturers to obtain FDA approval, a consideration not reflected in FDA's June 15 and 29, 2012 statements, JA273-74, JA277-78.

Thus, even where the approved drug lacks statutory exclusivity, CPG 440.100 allows only a limited grace period. Where, as here, the approved drug has statutory exclusivity, there should be no grace period as to new patients, or at most a minimal one. Makena's approval occurred, and its exclusivity period began running, more than two years ago. JA207-14. Despite FDA's statements, it has not "initiate[d]" any "enforcement action" to stop the distribution of uncustomized 17P. Plainly, FDA is not applying CPG 440.100 to such 17P.

CPG 460.200 is elaborated in FDA warning letters. "Typically, FDA will not exercise its enforcement discretion for compounded drugs that are essentially copies of FDA-approved, commercially available drugs when there is no patient-specific medical need to justify the difference."[9]

[9] FDA Warning Letter CIN-07-28792-06 (Dec. 1, 2006) at JA184. Brief of Amici Curiae Alere Women's and Children's Health, LLC and Interested Physicians in Support of Appellees and Affirmance ("Alere Brief") consistently ignores the limitation of lawful traditional compounding to patients with a "patient-specific medical need" that justifies the difference between the commercially available drug and the compounded drug. That limitation pre-dated 21 U.S.C. § 353a, enacted in Pub. L. No. 105-115, § 127, 111 Stat. 2296, 2328-30 (1997). *See* FDA Compliance Policy Guide § 7132.16 (Mar. 16, 1992) at JA101. It is part of FDA's current understanding of permissible compounding. *See* JA164 ("the medical need for the particular variation of the compound for the particular patient"). *See also*

> Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. . . . FDA is seriously concerned about the public health risks associated with the large-scale production of drug products by manufacturers not meeting the laws and regulations applicable to drug manufacturing.[10]

The Congressional Research Service understands CPG 460.200 as providing that FDA "will focus its enforcement efforts on compounding efforts that are akin to 'manufacturing' . . . ."[11]

Plainly, despite FDA's statements, it is not applying CPG 460.200 to uncustomized 17P, even though CPG 460.200's fundamental concern about the risks from commercial-scale "compounding," JA163-64, is heightened as to 17P because it must be sterile. Appellees cite no evidence that any FDA statement after the Statement has had any effect on distribution of uncustomized 17P, or on FDA's own actions.[12] FDA Brief 24 asserts that "FDA is not pursuing a 'policy of non-

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Thompson v. W. States Med. Ctr., 535 U.S. 357, 360-61 (2002) ("tailored to the needs of an individual patient").

[10] FDA Warning Letter NYK 2008-06 (Jan. 10, 2008), JA189-90.

[11] CRS, Federal Authority to Regulate the Compounding of Human Drugs 9 (Apr. 12, 2013), *available at* http://www.fas.org/sgp/crs/misc/R43038.pdf.

[12] FDA Brief 33 n.6 cites a June 2012 CMS bulletin, JA275. Nothing in the record suggests, and Appellees do not assert, that it has had any effect.

enforcement' regarding the compounding of 17P," but fails to cite any enforcement action intended to stop uncustomized "compounding" of 17P.[13]

None of the actions Appellees do cite sought to stop such "compounding."

FDA's June 29, 2012 letter to Wedgewood, JA279-81, reinforces the Statement by communicating a lack of intent to enforce. The letter is not captioned as a warning letter, which is a threat to enforce.[14] The letter does not even request a response from Wedgewood, as warning letters always do.[15] FDA sent the letter long after any grace period under CPG 440.100 had expired.

FDA's prior history with Wedgewood shows the letter's lack of seriousness. In 2003, FDA obtained a warrant to inspect Wedgewood's premises because it had reason to believe that Wedgewood was violating the FDCA and would resist an inspection. Wedgewood challenged FDA's inspectional authority and lost. *In re Establishment Inspection of Wedgewood Vill. Pharmacy, Inc.*, 270 F. Supp. 2d 525, 530-31(D.N.J. 2003) (summarizing evidence of Wedgewood's unlawful drug manufacturing and prior resistance to inspection), *aff'd sub nom. Wedgewood Vill.*

[13] Appellees assert that "FDA employs a risk-based approach," FDA Brief 23, but fail to consider CPG 440.100 and CPG 460.200's risk-based justification for enforcement against uncustomized "compounding."

[14] *See* FDA, Regulatory Procedures Manual § 4-1-1[:] Warning Letter Procedures, *available at* http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm (last updated Aug. 1, 2012).

[15] *Id.* § 4-1-10, ¶ 5. *See also*, *e.g.*, JA185, JA193.

Pharmacy, Inc. v. United States, 421 F.3d 263 (3d Cir. 2005). In 2006, FDA sent Wedgewood a warning letter referring to "serious violations of the [FDCA]" in that Wedgewood "produces finished drug products that are essentially copies of commercially available products, and . . . does not document a medical need for particular patients for these versions of otherwise commercially available products."[16]

Since FDA's Statement, Wedgwood apparently has engaged in the same conduct.[17] With this history as background, FDA's non-warning letter – weaker than its 2006 letter – conveys a lack of intent to enforce. Nothing in the record suggests, and Appellees do not assert, that FDA's letter has had any effect on Wedgewood's conduct. Therefore, the letter does not evidence any departure from the non-enforcement policy announced in the Statement.

FDA's investigation of 17P and related API (after the study KV commissioned), cited at FDA Brief 33, did not lead to any enforcement, even though FDA found deficiencies in the samples it tested. Although the samples passed some tests, all 16 API samples [100%] "failed the Makena NDA's limit for unidentified impurities." JA273. "Two of the 13 samples [of 'compounded' 17P]

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[16] FDA Warning Letter 06-NWJ-03 at 1, 3 (Oct. 31, 2006), *available at* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076147.htm.

[17] KV Brief 18 n.36.

[15.4%] failed to meet the standard for unidentified impurities in the Makena NDA," and one [7.7%] was subpotent. *Id.* "FDA's testing of the retained samples [of 'compounded' 17P from the laboratories in the KV-commissioned study] found that three of 26 samples [11.5%] failed the standard for potency . . . in the Makena NDA." *Id*. Nevertheless, FDA declined to act because it found no "major safety problems." *Id.*

The Makena NDA standards – which some samples of 17P and API failed – relate to the safety and effectiveness of this life-saving, sterile drug. Evidently, multiple violations of those standards are insufficient to induce FDA to act against the "compounded" versions it called into the market: "major safety problems" are necessary. Plainly, FDA is applying to 17P much weaker standards than it applies to Makena, as the Statement necessitates.

The import bulletin, JA253-61, cited at FDA Brief 33-34, addresses certain aspects of 17P API presented for import, but not its unapproved status or probable use for uncustomized "compounding." The bulletin is not an attempt to stop the manufacturing of 17P in the guise of compounding. Indeed, under the bulletin, FDA examines each 17P API shipment proposed for import, and knows that it appears to violate Section 355: an unapproved drug necessarily so appears, unless and until the contrary is shown. Nevertheless, FDA allows the imports, as the

Statement necessitates. Appellees do not assert that they have rejected any import of API for uncustomized "compounding" of 17P.

Appellees go outside the record to cite an FDA statement and a newspaper article about recent FDA inspections of "compounders," FDA Brief 31 n.5, 34, 36. The inspections followed the 2012 outbreak of fungal meningitis among patients who had received an injected preservative-free "compounded" drug that was supposed to be sterile, but was contaminated.[18] As of June 3, the outbreak had caused at least 382 meningitis cases, 354 other infections, and 58 deaths, in 20 States.[19] Among the many drugs recalled by the "compounder" involved was 17P.[20]

FDA's inspections were an after-the-fact attempt to address a problem Congress intended FDA to prevent by applying Section 355 to manufactured

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[18] *See* FDA Archive of Updates on Multistate Fungal Meningitis Outbreak, *available at* http://www.fda.gov/Drugs/DrugSafety/FungalMeningitis/ucm325037.htm#10512 (last updated Dec. 12, 2012).

[19] CDC Multistate Fungal Meningitis Outbreak Investigation, *available at* http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html (last updated June 3, 2013).

[20] *See* List of Recalled Products Related to Fungal Meningitis Outbreak, *available at* http://www.fda.gov/Drugs/DrugSafety/ucm322752.htm (last updated Oct. 11, 2012).

drugs.[21] The risks from "compounded" drugs are well documented.[22] Commissioner Hamburg recently testified: "[O]ver the past 20 years we have seen multiple situations where compounded products have caused deaths and serious injuries."[23] She further testified: "In addition, FDA believes that with noted exceptions, certain products are not appropriate for compounding under any circumstances. These products would include: 1) what are essentially copies of FDA-approved drugs, absent a shortage . . . ."[24]

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[21] H.R. Rep. No. 75-2139, at 2 (1938) ("New drugs are required to be adequately tested for safety before they are placed on the market."). The addition of Section 355 to what became the FDCA resulted from numerous deaths caused by an improperly formulated drug. *See* David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 Law & Contemp. Probs. 2, 20, 40 (1939). Alere's view that physicians should have a choice between approved and unapproved drugs so that patients commonly would consume unapproved drugs, Alere Brief 2, would subvert Section 355 entirely.

Alere also fails to distinguish between HPC manufactured in compliance with FDA requirements and uncustomized 17P. The studies discussed at *id.* at 11-12 were not of any compounded product; those discussed at *id.* at 15-17 were not prospective, and FDA has not reviewed them. Concerning the cited studies and Makena's inclusion of a preservative, which FDA approved, *see* Second Declaration of Michael Jozwiakowski (Doc. 14-1 July 31, 2012).

[22] *See* KV Brief 14 & nn.26, 27.

[23] Statement of Margaret A. Hamburg, M.D., Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce 2 (Apr. 16, 2013), *available at* http://docs.house.gov/meetings/IF/IF02/20130416/100668/HHRG-113-IF02-Wstate-HamburgM-20130416.pdf.

[24] *Id.* at 10.

Yet, FDA unleashed uncustomized 17P to substitute for Makena. Like the "compounded" drugs in the meningitis outbreak, 17P is an injectable drug that is supposed to be sterile. FDA's recent inspections found violative conditions at all 28 "compounders" that were producing supposedly sterile drugs; and, to inspect Wedgewood in January 2013, FDA again needed a warrant.[25] Non-sterility concerns about "compounded" injectable drugs continue. Numerous recalls of such drugs have occurred.[26] One last month by a Tennessee "compounder" involves at least twenty reported infections in Florida, Illinois, and North Carolina.[27] Despite the name of the "compounder" – "Main Street Family Pharmacy" – its implicated preservative-free drug was used in multiple States.[28] NBC News reports: "FDA officials have repeatedly warned that it's a matter of

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[25] FDA, Summary: 2013 FDA Pharmacy Inspection Assignment (Apr. 11, 2013), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm347722.htm.

[26] *See* FDA website search results, http://google2.fda.gov/search?q=recall+and+compounding+and+drug&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&getfields=*&filter=1&requiredfields=-archive:Yes&ie=UTF-8&ip=173.226.64.254&access=p&sort=date:D:L:d1&entqr=3&entqrm=0&oe=UTF-8&ud=1&start=10.

[27] CDC, Multistate Investigation of Suspected Infections Following Steroid Injections (May 30, 2013), *available at* http://www.cdc.gov/hai/outbreaks/TN-pharmacy/index.html.

[28] *Id.*

when, not if, a new outbreak will occur because of poor regulation of compounding pharmacies."[29] These circumstances underscore Appellees' recklessness in authorizing distribution of uncustomized 17P by numerous "compounders" using product formulations and manufacturing facilities and methods FDA had never approved.

FDA Brief at 14, 15, 30-31 cites two KV press releases, issued, respectively, one business day after FDA's June 15 and 29, 2012 statements, JA273-74, JA277-78. The releases are not in the record.[30] Plainly, in a triumph of hope over realism, KV thought that FDA's statements "revers[ed]" the Statement and made it "outdated." KV erred.[31] FDA has not withdrawn the Statement,[32] and, as just shown, has done nothing inconsistent with it. As Wedgewood understands FDA's

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[29] Maggie Fox, NBC News, *FDA Warns of Infections Tied to Tenn. Pharmacy* (May 24, 2013), *available at* http://vitals.nbcnews.com/_news/2013/05/24/18472162-fda-warns-of-infections-tied-to-tenn-pharmacy.

[30] They are *available at* Press Release, KV Pharmaceutical, FDA and CMS Issue Important Updates on Makena® (June 18, 2012), http://www.kvph.com/news_center_article.aspx?articleid=359; Press Release, KV Pharmaceutical, FDA Issues Further Guidance About Makena® (July 2, 2012), http://www.kvph.com/news_center_article.aspx?articleid=362.

[31] KV adopts the formulations of confessions of error in *McGrath v. Kristensen*, 340 U.S. 162, 177-78 (1950) (Jackson, J., concurring).

[32] It remains on FDA's website, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2011/ucm249025.htm (last visited June 4, 2013).

June 15, 2012 statement announcing the results of FDA's investigation of 17P and related API: "The FDA found no reason to change its enforcement policies regarding compounded [17P]." JA276. The understanding of that statement by "compounders," not KV, is what matters in the marketplace.

In sum, FDA's Statement remains effective in the marketplace. FDA's statements and actions amount to ongoing implementation of the Statement's general policy of non-enforcement against unlawful distribution of uncustomized versions of 17P unless FDA learns that they present "major safety problems."

4. The Relief KV Seeks Is Consistent with *Chaney*.

Contrary to FDA Brief 21-22, the relief KV seeks fully protects the zone of enforcement discretion *Chaney* recognized. As KV Brief 28-29 explains, FDA would retain authority to make enforcement decisions in individual cases. Moreover, FDA's recent inspections surely already provide a basis, and reduce the FDA resources needed, for actions (*e.g.*, warning letters) against uncustomized 17P. Because FDA reviews every proposed import of unapproved 17P API, *see* JA253-61, little additional effort is needed to refuse admission of such API, as required by Section 381(a), unless it is shown to be for traditional compounding.

5. FDA's Statement Is an Abdication of Responsibility.

Contrary to FDA Brief 32-33, *Adams v. Richardson*, 480 F.2d 1159 (D.C. Cir. 1973) (en banc) (per curiam), applies here. *See* KV Brief 36-39. Its

applicability results from (i) FDA's and CMS's coordinated statements, JA038 (¶ 83), which, together, authorize the spending of federal money for products whose distribution violates the FDCA, and (ii) FDA's encouragement of such distribution and the consequent importation of unapproved 17P API, contrary to Sections 360cc(a), 353a, 355(a) and 381(a), unless FDA learns of "major safety problems." Neither *Chaney*, 470 U.S. at 833 n.4, nor *Cutler v. Hayes*, 818 F.2d 879, 892-94 (D.C. Cir. 1987), limits *Adams* to civil-rights cases.

FDA Brief 33 quotes *Cutler*'s statement that the FDCA "imposes no clear duty upon FDA to bring enforcement proceedings to effectuate either the safety or the efficacy requirements of the Act," 818 F.2d at 893. Here, however, additional FDCA provisions, not at issue there, and additional factual circumstances, including federal spending for unlawful products, distinguish this case from *Cutler*. *See* KV Brief 40. Moreover, *Cutler* involved a twelve-month deferral of enforcement while the administrative record remained open for additional submissions and FDA prepared a final monograph that would specify which drugs would be lawful and which not. *See* 818 F.2d at 899-901. Here, FDA has abandoned enforcement indefinitely, not deferred it temporarily. As the Court there stated when discussing unreasonable delay, "the agency lacks authority to simply do nothing to effectuate the purpose of the Act." *Id.* at 895. Here,

Appellees' active solicitation of unlawful distribution is even more clearly unauthorized.

B. *Chaney*'s Presumption of Unreviewability Is Rebutted Here Because the Factors Supporting Enforcement Discretion Are Absent.

FDA Brief 24 misconstrues the argument at KV Brief 41-42. That argument refers to destruction of KV's property right because a principal rationale for *Chaney* is that "when an agency refuses to act it generally does not exercise its *coercive* power over an individual's liberty or property rights, and thus does not infringe upon areas that courts often are called upon to protect." 470 U.S. at 832. Here, FDA deliberately has destroyed KV's property right, and thereby infringed on an area courts often are called upon to protect. In *Chaney*, FDA's inaction did not exercise power over liberty or property rights; FDA merely declined to provide a federal remedy against state action, and left the *status quo* unchanged.

KV Brief 42 cites *Center for Auto Safety v. Dole*, 828 F.2d 799, 803 (D.C. Cir. 1987), for the proposition that *Chaney*'s presumption is rebutted where discretionary factors are absent. FDA Brief 24-25 notes that, there, a regulation removed discretion, and argues: "No such regulations are present here." That argument fails. *Dole* treated EPA's regulation as "the legal equivalent of a statutory standard for *Chaney* purposes." 828 F.2d at 803. Here, discretion is removed by the statutes discussed at KV Brief 42-49. Moreover, a binding

advisory opinion excludes FDA discretion to consider price in drug-related decision-making. KV Brief 9 & n.18.

II. FDA'S STATEMENT IS REVIEWABLE UNDER THE ADMINISTRATIVE PROCEDURE ACT.

A. The FDCA Provides Law To Apply.

Contrary to FDA Brief 24, Congress has denied FDA discretion to call forth new violations of the FDCA in circumstances like those here. As KV Brief 42-49 explains, a court can review FDA's Statement, and hold that it constitutes an unlawful effective approval of uncustomized 17P. The coordinated actions of FDA and CMS induced and procured violations of the FDCA.

B. The Relief KV Seeks Is Authorized by Law.

General principles of equity support the requested relief. KV Brief 49-51. Although the two cases discussed at FDA Brief 36, which were cited for a more general point, did not involve enforcement against third parties, *Adams v. Richardson* did.

III. KV'S DUE PROCESS ARGUMENT WAS IMPROPERLY REJECTED.

KV Brief 3 n.3 noted that, in rejecting KV's due process argument as waived, the district court overlooked the argument presented in KV's memorandum supporting its motion for preliminary relief. The KV Brief addressed the issue in a footnote because the district court did not decide its merits,

and plainly erred because the argument was presented, with supporting authorities, to the court, JA056-57.

Washington Legal Clinic for the Homeless v. Barry, 107 F.3d 32, 39 (D.C. Cir. 1997), cited at FDA Brief 35 n.7, is distinguishable. There, appellants argued the merits, not that the district court erroneously had treated an issue as waived; and appellants presented their argument only in a footnote to the "Conclusion" section of their brief, and did not addressed it in their reply brief. Here, KV argues against a plainly erroneous finding of waiver; KV presented the argument early in its opening brief, and addresses it in this reply brief. Moreover, Appellees are not prejudiced by the way the argument has been presented.

IV. COUNT IV STATES A CLAIM UNDER SECTION 381(a).

A. KV Challenges Final Agency Action.

The final agency action Count IV challenges is FDA's Statement, a necessary component of which, albeit unacknowledged, is allowance of imports of unapproved API for uncustomized 17P. FDA Brief 42 recognizes that all such 17P depends on such imports.

B. Section 381(a)'s Text Precludes Discretion To Admit an Import that Appears To Violate Section 355.

Appellees' textual analysis of Section 381(a) and the asserted analogy to *Chaney*'s textual analysis, FDA Brief 38-39, fail. *See* KV Brief 52. Language such as "shall be imprisoned" specifies a criminal sentence: it is addressed to a

judge. Section 381(a)'s "shall" clause is addressed to those controlling imports – FDA and Customs and Border Protection. It thus provides law applicable to them.

Appellees argue that "the 'shall be refused admission' language describes the consequences that follow if FDA makes a determination that 'it appears' that one of the Act's requirements has been violated." FDA Brief 40. Not so. The "appears" clause refers neither to FDA nor to any determination, but, rather, to an objective circumstance. Where an article objectively appears to be in violation, the statutory text excludes FDA discretion to permit its importation by refusing to determine that it so appears.

Chaney distinguished *Dunlop v. Bachowski*, 421 U.S. 560 (1975), on the ground that, there, the objective statutory standard of "probable cause" withdrew discretion and provided law to apply. 470 U.S. at 833-35. In Section 381(a), the "appears" standard does the same, as did the statutory standards considered in *Armstrong v. Bush*, 924 F.2d 282, 295-96 (D.C. Cir. 1991).

The text of Section 381(a) ("If it appears . . . that") contrasts with that of Section 381(b) ("If it appears to the Secretary of [HHS] that"). Thus, Congress included deferential language in subsection (b) – <u>but not in subsection (a)</u>. Moreover, "shall be refused admission" in Section 381(a) contrasts with "may be refused admission" in Section 381(*o*); *see also* Section 381(d)(3)(B) ("the Secretary may refuse admission"). These contrasts reinforce the objectivity of the

standard and the plain meaning of "shall" in the third sentence of Section 381(a), which also serve the manifest purpose of Section 381(a): to protect the public from imports that apparently violate the FDCA.

The cases FDA Brief 39 cites are distinguishable. In each, the statute containing "shall" conditioned the agency's duty to act on an antecedent agency finding or determination. *See City of Seabrook v. Costle*, 659 F.2d 1371, 1373-74 (5th Cir. Unit A Oct. 1981) ("Whenever . . . the Administrator finds . . . , the Administrator [or he] shall"); *Dubois v. Thomas*, 820 F.2d 943, 946 (8th Cir. 1987) (same); *Wood v. Herman*, 104 F. Supp. 2d 43, 46 (D.D.C. 2000) ("If . . . the Secretary determines . . . he shall"), *aff'd on other grounds sub nom. Wood v. Dep't of Labor*, 275 F.3d 107 (D.C. Cir. 2001). The third sentence of Section 381(a) has no such language.

Her Majesty The Queen v. EPA, 912 F.2d 1525 (D.C. Cir. 1990), cited at FDA Brief 40, is distinguishable. It involved Clean Air Act § 115, not the FDCA. Section 115 was triggered only "[w]henever the Administrator . . . has reason to believe" a specified circumstance exists. Section 381(a) contains no analogous language. A further precondition for Section 115's remedy was an additional finding by the Administrator. 912 F.2d at 1528. Section 381(a) imposes no such additional precondition. At issue there was whether a further precondition for making those findings applied. *Id.* No such issue arises here. Finally, the Court

found a critical statutory ambiguity, and deferred to EPA's interpretation. *Id.* at 1533. No such ambiguity exists here.

C. KV's Interpretation Permits Imports for Lawful Compounding, To Remedy Shortages, and for Personal Use.

Section 381(a) prohibits importation of unapproved API for compounding unless it is shown that the compounding will be lawful under 21 U.S.C. § 353a. Section 353a provides an exception to the general scheme of Section 355, which, with limited exceptions, prohibits unapproved new drugs from interstate commerce.[33]

Contrary to FDA Brief 42, the relief KV seeks would permit imports of unapproved API for lawful traditional compounding, as KV Brief 54-55 explains. The importation would be authorized by the authorities discussed at KV Brief 48 n.60, including regulations under 21 U.S.C. § 353a(d)(2). Therefore, FDA Brief 45 errs in asserting that, "if section 381(a) is read in the mandatory manner in which plaintiffs suggest, FDA would be required to refuse admission to all unapproved [APIs] for use in compounding of any drug."

[33] FDA Brief 9 argues that the circuit split concerning the severability of Section 353a's unconstitutional provisions from its other provisions, *see* KV Brief 12, has created "uncertainty about the extent to which courts will apply section 353a." Any such uncertainty is irrelevant here. With or without Section 353a, commercial-scale distribution of an unapproved "compounded" drug violates 21 U.S.C. §§ 355(a), 331(d). FDA's June 29, 2012 statement acknowledges that FDA can enforce against such "compounded" drugs. JA277. FDA's recent inspections, *supra* pp. 17-20, demonstrate FDA's authority over uncustomized "compounding."

The argument at FDA Brief 45-46 concerning Section 353a(d)(2) fails because it depends on Appellees' assertion that "the exemptions in section 353a only apply to 'drug products,'" FDA Brief 45. Although subection (a) applies only to drug products, subsections (b)(1)(A) and (d)(2) apply to "drug substances," which are not "drug product[s]," *see* 21 C.F.R. § 314.3(b) (defining those terms). Subsection (d)(2) requires FDA to list unapproved "drug substances that may be used in compounding." An API so listed ordinarily would not appear to violate Section 355, unless the quantity suggests manufacturing. Therefore, Section 381(a) ordinarily would not bar its importation.

Contrary to FDA Brief 43, the procedure KV Brief 54-55 describes does not intrude on FDA's enforcement discretion, and is not precluded by *Chaney*. The procedure is one means, among others, by which FDA could substantially restore the pre-Statement *status quo*. FDA would retain discretion as to how to achieve that objective.

FDA Brief 43 fails to acknowledge that, under 21 C.F.R. § 1.94(a) (2012), the so-called "hearing" may consist merely of one written submission. The consignee or broker has no incentive to encumber the proceeding. Appellees provide no information on the number of such "hearings" or their burdensomeness.

The argument at FDA Brief 44 that FDA "would often be unable to determine" whether a given shipment would be used for lawful compounding fails.

Once a proposed import appears to be unlawful, the burden is on the consignee or broker to show the contrary. A pharmacy or distributor consignee or a broker has adequate incentive to gather in advance, and present to FDA, evidence that the proposed import is lawful. If FDA is not persuaded – if the appearance of a violation remains – Section 381(a) requires refusal of admission.

The argument at FDA Brief 46 n.13 fails to show that the other authorities discussed at KV Brief 48 n.60 collectively are inadequate to address shortages. The additional requirements for treatment use of investigational drugs can be satisfied sometimes: 21 C.F.R. §§ 312.310, 312.315, and 312.320 (2012) authorize treatment use for patient populations of all sizes.[34] Appellees do not address 21 U.S.C. § 360bbb(a), cited at KV Brief 48 n.60. It broadly authorizes FDA to permit shipments of "investigational drugs" for emergency treatment.[35]

The argument at FDA Brief 47 concerning 21 U.S.C. §§ 360bbb-3 and 381(d)(2) is misdirected. KV Brief 48 n.60 argues only that those provisions can apply to "some," not all, shortages. The point of footnote 60 is that, with KV's

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[34] *See generally* FDA, Draft Guidance for Industry[:] Expanded Access to Investigational Drugs for Treatment Use — Qs & As (May 2013), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf.

[35] *See generally* FDA, Emergency Use of an Investigational Drug or Biologic – Information Sheet, *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm (last updated Aug. 30, 2011).

proposed interpretation of Section 381(a), FDA can use a variety of tools to remedy drug shortages. Appellees fail to describe any scenario those tools collectively cannot remedy.

Appellants' proposed interpretation of Section 381(a) would allow imports for personal use. *See* KV Brief 55 n.68.

Finally, FDA Brief at 38, 47 misinterprets the cited footnote in a brief below. That footnote addressed FDA's discretionary decision whether to examine a proposed import. If it appears, however, that a drug proposed for import is unapproved and not exempted from Section 355, it "shall be refused admission."

CONCLUSION

Were FDA's Statement unreviewable, strategically positioned individual Members of Congress could pressure FDA to destroy statutory exclusivity whenever they object to the conduct of a manufacturer of a drug entitled to exclusivity. That would be bad for the proper administration of the FDCA, for consumers, and for FDA. Reviewability would give FDA grounds to resist such improper pressure.

More generally, were *Chaney* expanded to protect from judicial review not only refusals to enforce but also agencies' public invitations for new or increased violations of the statutes they administer, the ability of courts to ensure agency compliance with those statutes would be significantly diminished.

For the foregoing reasons, the district court's judgment should be reversed and the case remanded for further proceedings.

Respectfully submitted,

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Dated: June 12, 2013.

CERTIFICATE OF COMPLIANCE
WITH TYPEFACE AND WORD-COUNT LIMITATIONS

I, Richard M. Cooper, counsel for appellants and a member of the Bar of this Court, certify, pursuant to Federal Rule of Appellate Procedure 32(a)(7)(B), that the attached Corrected Reply Brief of Appellants K-V Pharmaceutical Company and Ther-Rx Corporation is proportionately spaced, has a typeface of 14 points, and contains 6,995 words.

s/Richard M. Cooper
Richard M. Cooper

June 12, 2013

CERTIFICATE OF SERVICE

I, Richard M. Cooper, counsel for appellants, certify that, on June 12, 2013, a copy of the attached Corrected Reply Brief of Appellants K-V Pharmaceutical Company and Ther-Rx Corporation was filed electronically through the appellate CM/ECF system with the Clerk of the Court. I further certify that all parties required to be served have been served.

s/Richard M. Cooper
Richard M. Cooper

June 12, 2013